REMARKS

Status of the Claims

Claims 1, 2, 8-12, and 41-48 are now pending in the present application, Claims 3-7 and 13-40 having been cancelled due to a restriction requirement. Applicants have amended Claims 1 and 8, to more clearly define the present invention, and added new Claims 41-48, as set forth above.

Claims Rejected under 35 U.S.C. § 112

The Examiner has rejected Claims 1, 2, and 8-12 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner requires clarification for a number of different terms employed in the claims. Appropriate amendments have been made.

With respect to Claims 1 and 8, the element of "at least one of physical and chemical attachment" has been eliminated. The term "predetermined" has also been eliminated from Claims 1 and 8.

Also with respect to Claims 1 and 8, the term "unique combination" has been amended, so that the claim now recites that "*a unique combination of the at least one carrier and the at least one reporter is achieved in each reaction vessel.*" Each reaction vessel thus includes a unique combination of carrier(s) and reporter(s). If reaction vessel 1 includes carrier 1 and reporters A and B, no other reaction vessel will contain the identical combination of carrier 1 and reporters A and B.

Claims 1 and 8 each recite a library of optically distinct reporter labeled carriers. The Examiner has correctly identified such a library as being related to a library of beads (as opposed to a library of chemical compounds). Applicants respectfully submit that the term "bead" implies a substrate having a specific shape, whereas the term "carrier" does not imply any specific shape, although bead shaped carriers are certainly encompassed by the term carrier.

With respect to the Examiner's question as to how Claim 2 further limits Claim 1, applicants have amended Claim 1 to more clearly recite that it is the reporters that are optically distinct. As recited in Claim 1, optically distinct reporters are attached to carriers to achieve optically distinct reporter labeled carriers. Claim 2 indicates that the carriers can also be optically distinct, as is discussed in the specification in conjunction with FIGURE 5.

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The Examiner has indicated that the term "*optically distinct carriers*" is unclear, because the optical property of the carrier could refer to the structure of the carrier or to a coating of the carrier. Applicants respectfully note that the term "optically distinct" was selected to broadly cover both embodiments identified by the Examiner. Optically distinct carriers are shown in FIGURE 5, 7, and 8 of the current application. Applicants' specification describes one embodiment in which optically distinct carriers are identical carriers that are separated into different groups or pools, with a different fluorescent dye attached to each carrier in each different pool. Thus, carriers in pool 1 might be individually labeled with a red dye, while each carrier in pool 2 might be individually labeled with a green dye (see page 9, paragraph 2 of the present application). However, applicants did not intend carriers to be optically distinguished solely based on an attached dye or reporter. Applicants clearly state that carriers can be identified by "any other optically distinguishable trait" (page 9, line 22). Applicants further disclose that optically distinguishable characteristics include size, shape, color, color intensity and other properties, either alone or in combination (see page 4, lines 2-5; page 7, lines 7-9; and page 12, lines 21-25 of applicants' specification).

Applicants have added additional dependent claims 41-48, each reciting a different embodiment relating to the optical distinctiveness of the carriers. Thus, while "optically distinct carriers" is a broad term, the term is not indefinite. MPEP 2173.04 states that the breadth of a claim is not to be equated with indefiniteness.

Claims Rejected under 35 U.S.C. § 102 in View of Wang

The Examiner has rejected Claims 1 and 2 as being anticipated by Wang et al. (U.S. Patent No. 5,922,617). Wang discloses methods and apparatus for determining interactions between different components of the same or different type of composition. The apparatus includes arrays of samples in tracks, where light emitting labels are excited and emitted light detected. Various modifications can be made to the invention of Wang, such as using pre-prepared segments that may then be attached to a disk for assaying. The Examiner concludes that Wang discloses an equivalent to applicants' claimed invention. Applicants respectfully disagree for the following reasons.

As amended above, Claim 1 recites a method for preparing a library of optically distinct reporter labeled carriers. The disclosure of Wang, while relating to labeled beads, is not

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specifically directed to producing a library of carriers, but instead, is directed to preparing a library of compounds attached to carriers (which may be individually labeled).

Note in subparagraphs (d) and (e) of Claim 1, applicants recite first apportioning at least one carrier into each reaction vessel, followed by the step of apportioning at least one optically distinct reporter into each reaction vessel. Finally, the reporters in each reaction vessel are attached to the carriers, such that each reaction vessel includes a set of optically distinct reporter labeled carriers that is uniquely different from the optically distinct reporter labeled carriers of each other reaction vessel.

As described by Wang, beads are distributed into pits formed into a solid substrate. Those beads may or may not be specifically encoded with a reporter (column 13, lines 56-65). Wang does not disclose that such reporters are attached to the beads ***after*** the bead is placed into a pit. Wang clearly teaches that the reporter is attached to the bead ***before*** the bead is placed into a pit. Attaching a reporter to a bead ***before*** the bead is placed in a reaction vessel is not equivalent to applicants' steps of placing carriers in reaction vessels, placing reporters in reactions vessels, and then attaching the reporters to the carriers in the reaction vessels.

Wang teaches adding dyes to beads in an array (see column 5, lines 6-29; and column 7, lines 21-39). However, it is clear that Wang is discussing such dyes as being applied to compounds attached to the beads. Wang's array is used for evaluating changes to compounds attached to beads. The array is prepared, then exposed to a condition that can cause changes to the compounds bound to beads in the array. The dyes are configured to enable those compounds that have changed to be identified. Wang does not teach that each bead in his array must have attached to it a set of optically distinct reporters that is uniquely different from the set of optically distinct reporters attached to each other bead in the array.

While Wang teaches an embodiment wherein each individual bead in an array includes an identifier that is unique to that bead, i.e., which enables that specific bead to be located in the array, as discussed above, that identifier is already attached to the bead when the bead in placed in a specific pit in the array. Further, Wang explicitly refers to U.S. Patent No. 5,565,324 (see column 7, lines 15and column13, line 59) as disclosing exemplary unique identifiers for each bead. The identifiers described in the '324 patent are ***not optically distinct reporters***. The type of identifier described in the '324 patent is preferably an electrophoric group that can be

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analyzed by gas chromatography or mass spectroscopy. The '324 patent specifically teaches that fluorescent tags should not be used alone, but rather in combination with a tag that can be separated or detected by other means as well, because fluorescent tags alone cannot provide the required number of identifiers.

In view of the preceding comments, it is clear that Wang does not teach an array in which each bead in the array must include a unique set of optically distinct reporters, where the reporters are attached to the beads after the beads have been positioned in an array. The modifications that would be required to Wang to achieve the present invention are not taught or suggested in the cited art, and indeed, the '324 patent teaches away from a library that includes only optically distinct reporters. Accordingly, the rejection of Claims 1 and 2 as being anticipated by Wang should be withdrawn.

Claims Rejected under 35 U.S.C. § 102 in view of Dower

The Examiner has rejected Claims 1, 8, and 10-12 as being anticipated by Dower et al. (U.S. Patent No. 5,708,153). The Examiner correctly notes that Dowers discloses a split/add/pool (SAP) combinatorial technique to produce a library of related compounds. Applicants respectfully disagree that Dower's SAP technique is equivalent to the claimed invention.

A key difference between Dower's SAP technique and the present claimed invention is that as defined by applicants' Claims 1 and 8, the number of reaction vessels is selected *such that at least one reaction vessel is available for each unique member of the library to be constructed*, which is required, because in the present invention, the library is not constructed using the convention SAP technique wherein the contents of the reaction vessels are combined into a single reaction vessel and then separated into a plurality of vessels. Note that in FIGURE 1 of Dower, *n* carriers are apportioned into three reaction vessels. Compounds (preferably including labels) are added, and the contents of the reaction vessels are pooled into a single reaction vessel and then split into the original three reaction vessels. This process is repeated until a desired library is generated. In FIGURE 1 of Dower, a library of 27 different compounds is produced using three reaction vessels (four if you consider the reaction vessel in which the contents are pooled to be a separate vessel).

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As recited in Claims 1 and 8, to produce a library of 27 beads, each labeled with different optical reporters, 27 different reaction vessels would be required. Dower's technique employs fewer reaction vessels and is clearly not equivalent. The cited art simply provides no basis to conclude that it would have been obvious to modify Dower's SAP technique to employ one reaction vessel for each member of the library. Indeed, applicants' recited method is not an SAP process or equivalent to an SAP process. Accordingly, the rejection of Claims 1, 8, and 10-12 as being anticipated by Dower should be withdrawn.

Claims Rejected under 35 U.S.C. § 102 in view of Zarling

The Examiner has rejected Claims 8, 9, and 11 as being anticipated by Zarling et al. (U.S. Patent No. 5,674,698). Zarling discloses methods, compositions, and apparatus for performing sensitive detection of analytes, such as biological macromolecules and other analytes, by labeling a probe molecule with an up-converting label. The up-converting label absorbs radiation from an illumination source and emits radiation at one or more higher frequencies, providing enhanced signal-to-noise ratio and the essential elimination of background sample autofluorescence. The methods, compositions, and apparatus are suitable for the sensitive detection of multiple analytes and for various clinical and environmental sampling techniques. A plurality of different up converting dyes can be used. The Examiner concludes that Zarling discloses an equivalent invention. Applicants respectfully disagree for the following reasons.

The Examiner has noted that Zarling discloses a Terasaki plate (a plate including a plurality of individual sample wells). Thus, it appears that the Examiner considers the plurality of wells in a Terasaki plate to represent the recited library of optically labeled beads (in the recited plurality of reaction vessels). To achieve an equivalent invention, Zarling must teach that the Terasaki plate is filled by apportioning optically distinguishable carriers to each well, apportioning optically distinguishable reporters to each well, and then attaching the reporters to the carriers, such that each well includes a set of optically distinct reporter labeled carriers that is unique from the optically distinct reporter labeled carriers of each other reaction vessel.

First, it is not clear that Zarling discloses carriers that are themselves optically distinct. While the Examiner is correct in noting that Zarling discloses a dye molecule attached to an up-converting phosphor, Zarling clearly describes both the up-converting phosphor and up-converting dyes as "labels" to be attached to a probe (column 5, line 40-49). Zarling

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discloses that the labels can be up-converting phosphors, up-converting dyes, or a combination of an up-converting dye and an up-converting phosphor. Based on this teaching of Zarling, there is simply no basis to conclude that Zarling's up-converting phosphor is equivalent to applicants' recited carrier. Logically, Zarling's probes are more related to applicants' recited carrier, and the up-converting labels (phosphors and/or dyes) are related to applicant's optically distinct reporters, so that Zarling cannot function in accord with applicants' claimed invention.

Zarling also does not appear to teach the steps of apportioning optically distinguishable carriers to each well, apportioning optically distinguishable reporters to each well, and then attaching the reporters to the carriers. With respect to the Terasaki plates, Zarling discloses preparing a series of Terasaki plates containing serial dilutions of monodisperse 0.3 .mu.m up-converting phosphor particles (column 45, lines 57-61). Zarling explicitly discloses that because of the statistical and pipetting problems associated with small volumes with low particle concentrations, 2 to 4 replicates were prepared of each dilution (column 46, lines 31-34) . Thus, on a single plate, at least 2-4 wells have identical contents.

With respect to filling the wells on the Terasaki plate, Zarling does not teach that an optically distinct carrier is added to each well, and then an optically distinct reporter is added to the well. Instead, Zarling teaches adding optically distinct reporters (the phosphor) to the wells. Zarling does not teach attaching reporters to carriers within the wells (reaction vessels).

Finally, Zarling does not teach or suggest that the contents of each well is uniquely different (such that each well includes a set of optically distinct reporter labeled carriers that is unique from the optically distinct reporter labeled carriers of each other reaction well). As Zarling teaches that some wells are filled with identical dilutions, achieving wells that each include a unique set of optically distinct reporter labeled carriers is logically impossible without significant modification. Yet, there is no teaching or suggestion that would lead one of ordinary skill in the art to perform any such modification.

Zarling does not disclose an equivalent invention, nor is there any basis for concluding that the modifications required to achieve an equivalent invention would have been obvious. Accordingly, the rejection of Claims 8, 9, and 11 as being anticipated by Zarling should be withdrawn.

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Claims Rejected under 35 U.S.C. § 103 over Wang in view of Furka

The Examiner has also rejected Claims 8-12 under 35 U.S.C. § 103(a) as being obvious over Wang et al. (U.S. Patent No. 5,922,617) in view of Furka (WO 93/24517). The Examiner asserts that while Wang does not disclose optically distinct carriers, Furka discloses such carriers, and the Examiner concludes that it would have been obvious to combine the references to achieve the present claimed invention. Applicants respectfully disagree for the following reasons.

The Examiner asserts that the required motivation for the suggested combination of Furka and Wang can be found in a desire to eliminate the need for expensive sequenators. However, it is not clear that Wang's array requires the use of such a sequenator. If Wang's array can be utilized without such a sequenator, then it is not clear why one of ordinary skill in the art would have been motivated to perform the modifications.

Even if the combination suggested by the Examiner is performed, an equivalent invention is not achieved, because Wang does not disclose the steps of placing carriers in reaction vessels, placing reporters in reactions vessels, and then attaching the reporters to the carriers *in the reaction vessels*. As discussed in detail above, it is clear that Wang discloses placing already labeled carriers into each pit on a substrate.

Also as discussed above, Wang does not disclose an array in which each element in the array (well, pit, reaction vessel) must include a unique set of optically distinct reporter labeled carriers that is uniquely different from the optically distinct reporter labeled carriers of each other element in the array.

The modifications that would need to be applied to a combination of Furka and Wang to achieve the present claimed invention are not suggested in the cited art, and as noted above, the '324 patent teaches away from a library including only optically distinct reporters. Accordingly, the rejection of Claims 8-12 under 35 U.S.C. § 103(a) as being obvious over Wang in view of Furka should be withdrawn.

Patentability of New Claims

Claims 41-48 have been added to specify the different types of optical distinct carriers employed by the present invention. Such claims are fully supported by the specification, as

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noted above in response to the rejection of claims 2 and 9 as being indefinite. Claims 41-48 ultimately depend on either Claim 1 or Claim 8 and are patentable for at least the same reasons.

In view of the preceding amendments and remarks, it will be apparent that all claims in this case define a novel and non-obvious invention, and that the application is in condition for allowance and should be passed to issue without further delay. Should any further questions remain, the Examiner is asked to telephone applicant's attorney at the number listed below.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on July 8, 2003.

Date: July 8, 2003

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